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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/554,702	10/27/2005	Olivier Bezencon		9370

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DICKSTEIN SHAPIRO LLP
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EXAMINER	
HABTE, KAHSAY	

ART UNIT	PAPER NUMBER
1624	

MAIL DATE	DELIVERY MODE
07/25/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/554,702	BEZENCON ET AL.	
	Examiner	Art Unit	
	Kahsay Habte	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7 and 8* is/are rejected.

7)☒ Claim(s) *6* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No._____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/6/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-8 are pending in this application.

Information Disclosure Statement

2. Applicant's Information Disclosure Statement, filed on 03/10/2005 has been acknowledged. Please refer to Applicant's copies of the 1449 submitted herewith. Note that 3 WIPO references (BE, BF and BG) and 18 NPL documents (CF to CW) have not been considered, because applicants did not submit said references. Applicants are kindly requested to provide said references.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 8 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. In claim 8, it is recited a method for the treatment or prophylaxis of RAS-associated diseases comprising hypertension, congestive heart failure, ...or complications of treatment with immunosuppressive agents after organ transplantation, but the specification is not enabled for such a scope.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

The scope of the claims is not adequately enabled solely based on the inhibiting activity of rennin by the compounds provided in the specification. First, the instant claims cover 'diseases' that are known to exist and those that may be discovered in the future, for which there is no enablement provided. The use disclosed in the specification is as pharmaceutical compositions useful as rennin inhibitors in cardiovascular events and renal insufficiency and also as inhibitors of plasmepsins to treat malaria. The test procedure and in vitro assay is provided in the specification is disclosed at pages 30-31. It is concluded that "The IC_{50} values of all compounds tested are below 100 nM", however, there is nothing in the disclosure regarding how this *in vitro* data correlates to the treatment of the diverse disorders embraced the instant claims. The disorders encompassed by the instant claims (e.g. hypertension, renal failure, diabetic complications), some of which have been proven to be extremely difficult to treat. There is no reasonable basis for assuming that the myriad of compounds embraced by the claims will all share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent and there is

no basis in the prior art for assuming the same. Note *In re Surrey*, 151 USPQ 724 regarding sufficiency of disclosure for a Markush group.

The claims are drawn for example to 'treating **diabetic complications**', however, diabetic complications are very complex and different one from the other. For example, one can show that diabetic complications of diabetic mellitus (one type of diabetes) are different one from the other. A very common short-term complication of diabetes mellitus is hypoglycemia (abnormally low blood sugar levels). This complication can occur during treatment if the amount of food eaten and the amount of insulin taken are not balanced properly. Hypoglycemia is more common in people with Type I diabetes but can occur in people with Type II diabetes who take sulfonylurea drugs. Sulfonyurea drugs increase the production of insulin from cells in the pancreas. If untreated, hypoglycemia can cause seizures, which are involuntary muscle movements and/or decreased awareness of the environment due to overexcitement of nerve cells in the brain. Ketoacidosis (described in the section above) is an example of a short-term complication of diabetes.

High levels of sugar in the blood make it more difficult for the body to fight against infections. This can lead to infections of the urinary tract, which is the part of the body that deals with the formation and excretion of urine(pee). To excrete means to release from the body as waste. Skin infections can also result, as can vaginal yeast infections (a type of infection of the female reproductive organ). Small blood vessels throughout the body get damaged as a result of diabetes. Eye problems can develop as a

complication, such as retinopathy (also known as diabetic retinopathy), which is damage to the retina and the blood vessels that serve it. The retina is an area at the back of the eye that is sensitive to light. Blood vessels are tube-shaped structures that carry blood to and from the heart. Both large and small blood vessels also start to break down quicker in people with diabetes mellitus. Blood may also have a difficult time moving throughout the body as a result of diabetes mellitus.

Another complication is peripheral neuropathy (also known as diabetic neuropathy), which is damage to nerve fibers outside of the brain or spine. Peripheral neuropathy can cause a gradual loss of sensation starting at the hands and feet, which sometimes moves up the arms and legs. Loss of feeling and poor blood circulation makes the body more susceptible to ulcers (open sores) and gangrene (tissue death due to poor blood supply or infection of a wound.). Peripheral neuropathy can also cause dizziness when standing up as well as impotence in men. Impotence is an inability to maintain an erect penis.

Kidney damage can occur as a complication of diabetes mellitus, which can lead to kidney failure. The kidneys are two organs located on each side of the spine, behind the stomach. The kidneys filter (remove) wastes from the blood. The kidney damage may need to be treated by a kidney transplant or dialysis. Dialysis is a technique in which one is hooked up to a machine that performs the functions of the kidneys, removing wastes and extra water from the blood.

Another complication of diabetes mellitus is a higher risk for atherosclerosis, which is a narrowing of arteries (blood vessels that carry blood away from the heart).

Atherosclerosis can cause damage to large blood vessels, which is a major cause of stroke and coronary artery disease. A stroke is a burst artery (a type of blood vessel that carries blood away from the heart) or a blockage of an artery in the brain. Coronary artery disease is a narrowing of coronary arteries, which supply the heart with blood. The narrowing of coronary arteries causes heart damage. People with diabetes also have a greater chance to have increased levels of cholesterol, which can speed up the development of atherosclerosis. Cholesterol is a waxy, fatty substance found only in animal tissues.

High blood pressure, other heart disorders, and cataracts are additional complications associated with diabetes mellitus. Cataracts is a darkening of the lens in the eye. The lens is an organ located between the colored part of the eye, that bends light as it enters the eye. A very important issue for people with diabetes mellitus to be concerned about is good foot care. This is because one complication of diabetes mellitus is ulcers (open sores) on the feet. In severe cases, ulcers can develop into gangrene. Gangrene is death of a tissue, usually due to a loss of blood supply. If a foot sore develops, you should see the doctor immediately.

With good foot care, ulcers and infections can usually be prevented. Good foot care involves inspecting the feet and washing and drying the feet carefully. If the skin on the feet is dry, it is recommended to use a moisturizer to keep them moist. Good foot care also involves wearing comfortable shoes, not walking barefoot, cutting toenails straight across, and visiting the foot doctor regularly.

In regard to the treatment of myriad diseases in claim 8, the specification is not enabled for the treatment of said myriad diseases.

In regard to the prophylaxis, to this day the only means available is the treatment of patients suffering for example from diseases such as glaucoma, hypertension, etc., but not the prevention of a healthy patient from getting glaucoma, hypertension, etc. said in the first place.

It is recommended that applicants delete this claim to overcome this rejection.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the use of the invention. In view of the breadth of the claim, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims.

Double Patenting

4. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory

obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. Claims 1-5 and 7-8 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3-8 and 10-15 of copending Application No. 10/576,904. Although the conflicting claims are not identical, they are not patentably distinct from each other because there is significant

overlap between instant claims 1-5 and 8 and claims 1, 3-8 and 10-15 of copending Application No. 10/576,904. The compounds are the same except in the definition of M. The minor difference appears to be in the definition of M (side chain). Applicants recite M = H, cycloalkyl, aryl, heterocyclyl, or heteroaryl and the copending application recites for example M = aryl-O(CH2)vR5. One skilled in the art would not consider this minor difference as a patentable difference between the two applications. It does not require a complex organic technique to add a linker to the aryl group.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-5 and 7-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention:

a. In claim 1, the phrase "W is a six-membered, non benzofused, phenyl" is not clear. Is the recitation of "six-membered and non benzofused" refers only to phenyl? Or to both phenyl and heteroaryl? If it refers only to phenyl, it is recommended that applicants delete "six-membered and non benzofused" from the definition of W.

b. In claim 1, the phrase "solvent complexes or morphological forms" is not clear. What is covered and what is not? It is recommended that applicants delete this phrase.

Objection

7. Claim 6 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

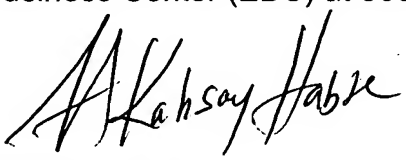
8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kahsay Habte, Ph. D. whose telephone number is (571) 272-0667. The examiner can normally be reached on M-F (9.00AM- 5:30PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should

you have questions on access to the Private PAIR system, contact the Electronic

Business Center (EBC) at 866-217-9197 (toll-free).



Kahsay Habte
Primary Examiner
Art Unit 1624

KH
July 19, 2007